August 16, 2006

Mr. John Morris
American Chemistry Council
Aliphatic Esters Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Morris:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Glycol Esters Category posted on the ChemRTK HPV Challenge Program Web site on March 25, 2004. I commend the Aliphatic Esters Panel for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Glycol Esters Category

Summary of EPA Comments

The sponsor, the American Chemistry Council's Aliphatic Esters Panel, submitted a test plan and robust summaries for the revised Glycol Esters Category, dated December 24, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on March 25, 2004. The category consists of 9 substances. Five analog substances were submitted to support the category.

1. Category Definition. The category is well defined. For data analysis purposes, EPA divided it into glycol monoesters, tri-and tetraethylene glycol diesters, and ethylene and propylene glycol esters.

2. Category Justification. Similarities in chemical structure and patterns in physicochemical properties and toxicity support the category. However, structural characteristics of category members and patterns of toxicity suggested dividing the category members into three smaller groups for evaluating the ecotoxicity and mammalian toxicity endpoints.

3. Analog Justification. Similarities among the category members and analogs generally support the use of the analogs.

4. Physicochemical Properties. The submitter needs to provide measured melting point data for six substances; measured vapor pressure data for four substances; and measured water solubility data for five substances.

5. Environmental Fate. The submitter needs to provide the input values used in its fugacity calculations. The submitter needs to recalculate its fugacity values using the measured melting point and vapor pressure values indicated above.

6. Health Effects. Adequate data, with supporting technical discussions, were provided for all SIDS endpoints for the glycol monoesters and ethylene/propylene glycol esters for the purposes of the HPV Challenge Program. For the tri- and tetraethylene glycol diesters, the submitter needs to provide a technical discussion for the reproductive/developmental toxicity endpoint. Predicted or known metabolic pathways need to be outlined, and available toxicity data for tri- and tetraethylene glycols need to be referenced. The submitter needs to address deficiencies in the robust summaries.

7. Ecological Effects. The data provided by the submitter for the sponsored and analog substances are considered inadequate for the purposes of the HPV Challenge Program. The submitter needs to provide data for at least one representative of the tri- and tetraethylene glycol diesters. Because the sponsored members of this group have log K_{ow} values in the range of 2.86 – 6.73 (measured and estimated), both acute and chronic testing should be considered.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments on the Glycol Esters Category Challenge Submission

General

Owing to the range in carbon number and diversity of the glycol units in the sponsored substances, EPA has grouped the category for review purposes into glycol monoesters, tri- and tetraethylene glycol diesters, and ethylene and propylene glycol esters.

Category Definition

The category is clearly defined. The sponsored glycol esters range in carbon number from C20 to C41, contain one, three, or four glycol units, and are shown below as grouped by EPA for review.

CAS No.	Substance
	Glycol monoesters
111-60-4	Stearic acid, 2-hydroxyethyl ester
67989-24-6	9-Octadecenoic acid, ester with 2,2-dimethyl-1.3-propanediol
	Tri-and tetraethylene glycol diesters
94-28-0	2-Ethylhexanoic acid diester with triethylene glycol
70729-68-9	Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester
68583-52-8	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol
18268-70-7	2-Ethylhexanoic acid, diester with tetraethylene glycol
	Ethylene and propylene glycol esters
627-83-8	Stearic acid, ethylene ester
105-62-4	Oleic acid, propylene ester
42222-50-4	9(Z)-Octadecenoic acid, 2,2-dimethyl-1,3-propanediyl ester

Category Justification

The submitter bases the grouping of these esters on the structural similarity of the ethylene, polyethylene, and propylene glycol substructures and their fatty acyl chains. The structures of the sponsored chemicals and analogs are consistent to the extent that all contain at least one glycol moiety and have at least one ester function. Nonetheless, the structures differ significantly in the length (C7-C18) of the carboxylate chains and the number of glycol units in the alcohol portion (1, 3, or 4 units). These differences are anticipated to result in a range of physicochemical properties, especially water solubility and octanol/water partition coefficient (log K_{ow}), along with associated environmental fate and toxicological properties. However, the submitted data suggest that there is a pattern of values consistent with the structure of the esters. Therefore, grouping the members into a single category is supported.

However, while the overall grouping of the sponsored chemicals is supported, there are distinct groupings within the category that affect the testing analysis. These groupings are based on the measured and estimated partition coefficients, molecular weights, common substructural features, and anticipated differences in the metabolism and toxicities of the esters. The range and pattern of partition coefficients and molecular weights of the glycol esters indicates that these chemicals can be divided into two groups. In the first group are the ethylene and propylene glycol diesters with log K_{ow} values >10 and molecular weights above 500, and in a second group are the tri- and tetraethylene glycol diesters and the glycol monoesters, both of which have log K_{ow} values of 2.8 to 8.4 and molecular weights below 500. For the mammalian toxicity endpoints, substances in the second group need to be considered as two subgroups, as the glycol monoesters contain a hydroxyl group and are therefore structurally distinct from the tri- and tetraethylene glycol diesters. Because of the hydroxyl function, the glycol monoesters may be metabolized differently than the tri- and tetraethylene glycol diesters. Therefore, for the purpose of evaluating data and testing needs, EPA is treating the category as three groups: glycol monoesters, tri- and tetraethylene glycol diesters, and ethylene and propylene glycol esters.

Analog Justification

Five analog esters were submitted. These esters range in carbon number from C15 to C39 and are identified as: heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS No. 71839-38-8), triethylene glycol, diheptanoate (CAS No. 7434-40-4), propylene glycol, monostearate (CAS No. 1323-39-3) and propylene glycol, dilaurate (CAS No. 22788-19-8), and propylene glycol, diisostearate (CAS No. 68958-54-3). The analogs have structures and molecular weights that span ranges similar to the sponsored substances and are considered appropriate analogs.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for boiling point and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Melting point. The estimated data provided by the submitter for CAS Nos. 70729-68-9, 67989-24-6, 68583-52-8, 18268-70-7, 105-62-4 and 42222-50-4 are not adequate because estimated data above 0 ºC are inadequate for the purposes of the HPV Challenge program. The submitter needs to provide measured melting point data for these chemicals according to OECD TG 102.

Vapor pressure. The estimated data provided by the submitter for CAS Nos. 94-28-0, 70729-68-9, 68583-52-8 and 18268-70-7 are not adequate because estimated values above 7.5×10^{-8} mm Hg are inadequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured vapor pressure data for these chemicals according to OECD TG 104.

Water solubility. The estimated water solubility values provided by the submitter are not adequate for the purposes of the HPV Challenge Program. Water solubility values above 1 µg/L must be measured according to OECD TG 105. Furthermore, the measured water solubility value of 30 mg/L provided by the submitter for CAS No. 7434-40-4 is 80 times larger than the calculated value of 0.3732 mg/L. This difference increases the probability that the estimated values for the other chemicals in the category may also be significantly different than measured values. The submitter needs to provide measured water solubility values according to OECD TG 105 for those chemicals with estimated values above 1 µg/L: CAS No.'s 111-60-4, 94-28-0, 70729-68-9, 68583-52-8 and 18268-70-7.

Environmental Fate (photodegradation, stability in water, biodegradation and fugacity)

The data provided by the submitter for photodegradation, stability in water and biodegradation are adequate for the purposes of the HPV Challenge Program.

Fugacity. The submitter needs to provide all input values used in the fugacity calculations. The submitter needs to recalculate its fugacity values using the measured melting point and vapor pressure values indicated above. EPA prefers that measured physicochemical property data be provided, both to characterize a substance and to provide inputs to transport-distribution models. The use of estimated values introduces uncertainties that then become magnified in modeling applications.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Given the differences in measured and estimated partition coefficients and water solubilities, molecular weights, substructural features, and potential for differences in metabolism and toxicity, EPA assessed the adequacy of health effects endpoint data independently for each group. Several studies were mentioned in the test plan in support of the technical discussion for reproductive/developmental toxicity. Robust summaries need to be prepared for these studies to support the technical discussion.

Glycol monoesters. Adequate data were submitted for all SIDS endpoints for the purposes of the HPV Challenge Program. The submitter needs to address deficiencies in the robust summaries.

Tri- and tetraethylene glycol diesters. Adequate data were submitted for the acute, repeated-dose and genetic toxicity endpoints. The submitter needs to address deficiencies in the robust summaries.

Reproductive/developmental toxicity. Data from 28-day oral studies are inadequate to address the reproductive toxicity endpoint. No data were submitted for the developmental toxicity endpoint. However,
triethylene and tetraethylene glycols have been assessed as part of the Ethylene Glycols Category in the OECD SIDS Program (http://cs3-hq.oecd.org/scripts/hpv/). This information needs to be referenced and incorporated into a technical discussion of the metabolism of tri- and tetraethylene glycol diesters. No treatment related-effects were reported in the 28-day oral repeated-dose toxicity study for CAS No. 70729-68-9, up to 1000 mg/kg/day, and the available oral toxicity data suggest that, even at the limit dose, no effects on reproductive/developmental toxicity would be expected. Therefore, EPA anticipates that no new information would be gained from further animal experimentation for the purposes of the HPV Challenge Program.

Ethylene and propylene glycol esters. Adequate data were submitted only for the acute toxicity endpoint. However, owing to the physicochemical properties (predicted log K_{ow} values >10, predicted water solubility values <1E-11 mg/L), but especially because of their high molecular weights (> 500) and accompanying low acute toxicity (> 5 g/kg), EPA recommends no further testing for the purposes of the HPV Challenge Program.

Ecological Effects (fish, invertebrates, and algae)

The data provided by the submitter for the sponsored and analog substances are considered inadequate because most results are reported using nominal loading rates without accompanying analytical data, and the tests seem to have been conducted above the water solubility limits of the tested substances. The submitter needs to provide data for at least one representative member of the tri- and tetraethylene glycol diesters. As the sponsored members of this group have log K_{ow} values in the range of 2.86 – 6.73 (measured and estimated), both acute and chronic tests should be considered. However, EPA is suggesting no further testing for the glycol monoesters or the ethylene and propylene glycol diesters because of their high log Kow values (7.26 or >8) and estimated low water solubilities (<1ppb).

Glycol monoesters. The data provided by the submitter for acute toxicity to fish, daphnia, and algae for CAS No. 71839-38-8 and acute toxicity to fish for CAS No. 67989-24-6 are considered inadequate because the results are reported using nominal loading rates without accompanying analytical data. The tests seem to have been conducted above the water solubility limit of the tested substance. However, EPA considers no further testing necessary for the monoesters because their log Kow values are high (7.26 and 8.4).

Tri- and tetraethylene glycol diesters. The data provided by the submitter for acute toxicity to fish, daphnia, and algae for the analog, CAS No. 7434-40-4, and the sponsored substance, CAS No. 70729-68-9, as well as acute toxicity to fish and daphnia for the sponsored substance, CAS No. 94-28-0, are inadequate. The submitter considered reliabilities to be low and the experimental information given in the studies was limited. Also, the tests seem to have been conducted above the water solubility limits of the tested substances. The submitter needs to provide adequate ecological endpoints data for at least one representative member of the tri- and tetraethylene glycol diesters. Finally, because the sponsored substances in this group have log K_{ow} values in the range of 2.86 – 6.73 (measured and estimated), chronic testing should be considered.

Ethylene and propylene glycol esters. No data were provided for the ecotoxicity endpoints for any of the sponsored or analog substances in this group. However, since all the log K_{ow} values are >8, no testing of these substances is requested.

Specific Comments on the Robust Summaries

Health Effects

General. Purity and/or percentage composition of test substances need to be clearly defined in the robust summaries for all category members.

Glycol monoesters: Genetic toxicity (gene mutations). For CAS No. 71839-38-8, the submitter needs to indicate, if available, why the highest concentration used was 1000 ug/plate of test material when guidelines recommend 5000 ug/plate.

Glycol monoesters: Reproductive/Developmental Toxicity. The submitter needs to provide robust summaries for the multi-generation studies referred to on p. 18 of the test plan that are used to support the technical discussion, including study details pertaining to reproductive and developmental toxicity endpoints.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.